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Taxane-containing chemotherapy in the treatment of early breast cancer patients

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In primary breast cancer, taxane-based compared with anthracycline-based adjuvant chemotherapy significantly reduces the relative risk of recurrence (ranging from 17% to 36%) and sometimes improves overall survival. Different dosages and schedules of anthracyclines and taxanes have been tested. Randomized studies comparing sequential versus concurrent administrations are in progress and no data about efficacy are available. However, based on a single randomized trial and on indirect comparisons, safety and tolerability seem to be better with sequential schema. A formal comparison between weekly and every 3 weeks administration of taxanes reported no substantial difference in terms of efficacy. However, taking into account a subgroup analysis of this study, and results coming from metastatic disease, the best way to give taxanes seems to be either weekly paclitaxel or docetaxel every 3 weeks. In the majority of the study, taxane efficacy seems to be independent of hormonal receptor status, i.e. active in both hormonal receptor positive and negative disease. In conclusion, taxane-based adjuvant chemotherapy is a standard option for most early breast cancer patients with node-positive disease. No sufficient and dedicated data are available in node-negative disease.

Key words: early breast cancer, adjuvant chemotherapy, taxanes

sequential or concomitant schedule: which is better?

Six randomized phase III trials (CALGB 9344 [1], NSABP B-28 [2], PACS 01 [3], GEICAM 9906 [4] and MDACC 94–002 [5]) (Table 1) evaluated the efficacy of taxanes given sequentially to anthracyclines compared with anthracyclines-based regimens as adjuvant chemotherapy for operable breast cancer. A total of nearly 10 000 node-positive patients entered these studies. CALGB 9344 and NSABP B-28 used, as the control arm, four cycles of standard doxorubicin–cyclophosphamide (AC), while PACS 01, GEICAM 9906 and MDACC 94–002 had a more adequate control arm (i.e. FE100C ×6, FE90C ×6, FA50C ×8, respectively). All these trials, with the exclusion of MDACC 94–002, demonstrated a statistically significant improvement in disease free-survival (DFS) in favor of taxanes-containing chemotherapy with a relative reduction of relapse ranging from 17% to 36% and with an absolute benefit of 4%–6%. Moreover, two studies (CALGB 9344 and PACS 01) also demonstrated a statistically significant benefit on overall survival with a relative reduction of risk of death of 18% (HR = 0.82, CI 95% 0.71–0.95; $P = 0.0064$; CALGB) and of 23% (HR = 0.77, CI 95% 0.59–1.00; $P = 0.017$; PACS 01), respectively. Grade 3–4 toxicity analysis of sequential schedules is shown in Table 2. Absolute increase (+) or decrease (−) in toxicity due to taxanes compared with control arms are reported. Sequential docetaxel is associated with more febrile neutropenia, edema and nail disorders, while sequential paclitaxel is associated with more neuropathy and arthralgia/myalgia.

Four randomized trials (BCIRG 001 [6], E2197 [7], RAPP 01 [8] and ECTO [9]) (Table 1) evaluated the efficacy of taxanes-based chemotherapy given concurrently with anthracyclines compared with anthracyclines-based chemotherapy. More than 5000 patients were enrolled. BCIRG 001 tested a triplet combination containing anthracyclines and taxanes given concurrently (TAC: docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) compared with FAC (fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) and demonstrated a statistically significant improvement both in DFS (HR = 0.72, CI 95% 0.59–0.88; $P = 0.001$) and overall survival (OS) (HR = 0.70, CI 95% 0.53–0.91; $P = 0.008$), with an absolute benefit of 7% and 6%, respectively. E2197 [7] compared AT (docetaxel) versus standard AC. No differences in both DFS (HR = 1.03, CI 95% 0.86–1.25; $P = 0.70$) and OS (HR = 1.09, CI 95% 0.85–1.40; $P = 0.49$) were observed. ECTO [9] was designed to study the addition of paclitaxel concurrently with anthracyclines (followed by cyclophosphamide, methotrexate and fluorouracil; CMF). At 31 months follow-up, a benefit in freedom from progression was observed in the paclitaxel arm (HR = 0.65, CI 95% 0.47–0.90; $P = 0.01$). No efficacy data are available for RAPP 01.

Table 3 shows grade 3–4 toxicity profile of concurrent paclitaxel and concurrent docetaxel. Absolute increase (+) or decrease (−) in toxicity due to taxanes compared with control arms are shown. Chemotherapy with combined anthracyclines and adequate doses of docetaxel (i.e. 75 mg/m^2) requires antibiotic prophylaxis and G-CSF support (13%–34% increase

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Table 1. Trials of adjuvant chemotherapy containing taxanes divided by sequential and concurrent schedules, by different taxanes schedules and by taxanes versus anthracyclines

Study	Random	FU[a]	No. of patients	Inclusion criteria	Median age	Premenopausal (%) or <50 years (%)	N ≥4 (%)	HR– (%)	HER2+ (%)	Disease-free survival	Subgroup analysis (benefit)	Overall survival
Sequential taxanes												
CALGB 9344 [1]	A (60/75/90) C 600 × 4 +/− P 175 × 4	69	3121	Node+	NR	60%	54%	34%	NR	HR 0.83 *P* = 0.0023	HR− only	HR 0.82 *P* = 0.0064
NSABP B28 [2]	AC (60/600) × 4 AC (60/600) × 4 – P 225 × 4	65	3060	Node+	NR	50%	30%	34% (ER−)	NR	HR 0.83 *P* = 0.006	HR+ only	HR 0.93 *P* = 0.46
PACS 01 [3]	FEC (500/100/500) × 6 FEC × 3 – D 100 × 3	60	1999	Node+	50	50%	38%	21%	NR	HR 0.83 *P* = 0.014	Postmenopausal N 1–3	HR 0.77 *P* = 0.017
GEICAM 9906 [4]	FEC (600/90/600) × 6 FEC × 4 (600/90/600) – wP100 × 8	47	1248	Node+	50	55%	38%	20%	15%	HR 0.64 *P* = 0.0009	Postmenopausal N 1–3 HR + and HR– HER2 + and HER2−	HR 0.74 *P* = 0.1375
MDACC 94–002 [5]	FAC (500 d1-8/50/500) × 8 P 250 × 4 – FAC × 4	60	524	Stage I–IIIB	NR	56%	34%	37% (ER−)	NR	HR 0.70 *P* = 0.09	Better benefit ER−	NR
Concurrent taxanes												
BCIRG 001 [6]	DAC (75/50/500) × 6 FAC (500/50/500) × 6	55	1491	Node+	49	56%	38%	24%	21%	HR 0.72 *P* = 0.0010	N 1–3 HR+ and HR- HER2 + and HER2−	HR 0.70 *P* = 0.0080
ECTO [9]	A × 4 – CMF × 4 AT × 4 – CMF × 4 AT × 4 – CMF × 4 (PST)	31	1355	T >2 cm	NR	44%	NA	31%	NR	HR 0.66 *P* = 0.01	HR – for PST	HR 0.71 *P* = 0.71
E2197 [7]	AT (60/60) × 4 AC (60/600) × 4	53	2952	N 1–3 Node – and T >1 cm	51	NR	NR 65% N-	35% (ER−)	NR	HR 1.03 *P* = 0.70	Better benefit HR− ER+ PR-	HR 1.09 *P* = 0.49
RAPP 01 [8]	AC (60/600) × 4 AT 60/75) × 4	24	627	N 1–3 N- High risk	52	47%	0%	19%	11%	NR	NR	NR
Different taxane schedules												
INT E1199 [14]	AC (60/600) ×4, followed by P 175 × 4 wP 80 × 12 D 100 × 4 wD 35 × 12	46	4988	Node + Node- and T ≥2 cm	51	46%	33%	27%	20%	P versus D HR 0.985 *P* = 0.83 q3w versus w HR 1.043 *P* = 0.54	Better trend with Weekly Paclitaxel 3-weeks Docetaxel	NS (HR not reported)
AC-P versus AP-wP [15]	AC (60/600) × 4 – P 175 × 4 AP (50/200) × 4 – wP 80 × 12	36	1830	N+ N− and T >2 cm HR+ N− and T >1 cm HR−	52	33%	27%	35%	NR	HR 0.74 *P* = 0.050	NR	HR 0.65 *P* = 0.005
Taxanes versus anthracyclines												
USOR [16]	AC (60/600) × 4 DC (75/600) × 4	60	1016	Stage I–III (Stage III: 7%)	52	NR	11%	28%	NR	HR 0.67 *P* = 0.015	NR	HR 0.76 *P* = 0.131

A, adriamicin; C, cyclophosphamide; P, paclitaxel; wP, weekly paclitaxel; F, fluorouracil; E, epirubicin; D, docetaxel; wD, weekly docetaxel; M, methotrexate; PST, primary systemic therapy.

[a]FU, median follow-up; NR, not reported; NA, not applicable; NS, not significant; N, number of positive nodes; HR−, hormonal receptor negative; ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; q3w, schedules every 3 weeks; w, weekly schedules.

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Table 2. Grade 3–4 toxicities of sequential anthracyclines and taxanes (docetaxel and paclitaxel) compared to non-taxanes regimes

Grade 3–4 toxicity	Sequential docetaxel FEC-D [3]	Sequential paclitaxel AC-P [1, 2, 4]
Febrile neutropenia	+4%	+3%–7%
Infection	+0%	+1%
Nausea-Vomiting	−9%	−29% (also grade 2)
Stomatitis	+2%	−9% (also grade 2)
Nail disorders	+9%	NR
Edema	+4%	NR
Neurosensory–neuromotor	+0%	+3%–18%
Arthralgia/myalgia	NR	+2%–12%
Cardiac	−1%	−0.1%–0.4%
Toxic deaths	+0%	−0.2%

Table 3. Grade 3–4 toxicities of concurrent anthracyclines and taxanes (docetaxel and paclitaxel) compared with non-taxanes regimens

Grade 3–4 toxicity	Concurrent docetaxel DAC [6]; $A_{60}D_{60}$ [7]; $A_{60}D_{60}$ [8]	Concurrent paclitaxel AP-CMF [9]
Febrile neutropenia	+13%–34%	+2%
Anemia requiring transfusions	+3%	+0%
Infection	+2%	+1%
Vomiting	−4%	NR
Stomatitis	+3%–5%	+0.5%
Nail disorders	+2%	NR
Edema	+0.5%	NR
Neurosensory–neuromotor	+0	+1% (+15% grade 2)
Arthralgia/myalgia	+0.5%	NR
Cardiac	+0.5%	−0.2%
Toxic deaths	+0.3%–0.6%	+0%

Table 4. Taxanes efficacy related to hormonal receptor status (data are reported as hazard ratio and 95% CI)

Study	HR−	HR+
BCIRG 001	0.69 (0.49–0.97)	0.72 (0.56–0.92)
GEICAM 9906	Significant	Significant
CALGB 9344	0.72 (0.59–0.86)[a]	0.91 (0.78–1.07)
E 2197	1.21 (0.92–1.59)[b]	0.99 (0.75–1.30)[b]
NSABP B-28	0.77 (0.65–0.92)	0.90 (0.72–1.12)

HR−, hormonal receptor negative, estrogen and progesterone.
HR+, hormonal receptor positive, estrogen and/or progesterone.
[a]Hormonal receptor negative or unknown.
[b]Data referred to ER− instead of HR− and to ER+ instead of HR+.

in febrile neutropenia) and is also associated with more anemia, stomatitis and nail disorders. Furthermore, RAPP 01 [8] trial was prematurely closed because of higher risk of life-threatening complications with doxorubicin–docetaxel regimen (AT) compared to doxorubicin–cyclophosphamide (AC), in particular febrile neutropenia (40.8% versus 7.1%, $P < 0.001$), with three deaths in the AT arm (doses: adriamicin 60 mg/m^2, docetaxel 75 mg/m^2 every 3 weeks). Of note, antibiotic prophylaxis was not given in this study. The addition of paclitaxel, concomitantly with anthracyclines at full doses (paclitaxel 200 mg/m^2 concurrent with doxorubicin 60 mg/m^2 every 3 weeks) significantly increased grade 2–3 neuropathy (grade 2: 20.5% versus 5.0%; grade 3: 1.3% versus 0.2%) and marginally increased febrile neutropenia.

Overall, no efficacy data exist on direct comparison between sequential and concurrent schedules. Only one study, BCIRG 005 [10], compares TAC regimen with AC followed by docetaxel and, actually, only data about toxicities are known: TAC is associated with a statistically significant increased febrile neutropenia (17.9% versus 8.5%).

All taxanes schedules improve disease free-survival but taxanes administered sequentially to anthracyclines appear to be less toxic and more manageable than concurrent administration.

which taxane is better: paclitaxel or docetaxel? Weekly or every 3 weeks?

In metastatic breast cancer, paclitaxel showed a different activity if given with a 3-week or with a weekly schedule. CALGB 9840 [11] compared two different schedules of paclitaxel: 80 mg/m^2 on days 1, 8, 15 every 28 days and 175 mg/m^2 every three weeks every 21 days. Results of this study demonstrated a statistically higher activity of weekly schedule in terms of response rate (40% versus 28%; HR = 1.61, $P = 0.017$) and time to progression (9.0 months versus 5.0 months; HR = 1.45, $P = 0.0008$). Overall survival was not significantly different (24 months versus 16 months; HR = 1.19, $P = 0.17$). Another study [12] was designed to evaluate activity and efficacy of docetaxel given weekly or every 3 weeks (doses: 40 mg/m^2 weekly consecutively for 6 weeks every 8 weeks compared to 100 mg/m^2 every 3 weeks). Results showed no difference in terms of activity (response rate: 34% versus 33%), time progression (5.7 versus 5.3 months) and median overall survival (29.1 versus 20.1 months). In the metastatic setting, a randomized phase III trial also compared docetaxel and paclitaxel [13]. Median overall survival (15.4 versus 12.7 months; HR = 1.41, $P = 0.03$), median time to progression (5.7 versus 3.6 months; HR = 1.64, $P < 0.001$), were reported to be better for the docetaxel arm.

Data in early breast cancer were recently presented at S. Antonio Breast Cancer Symposium 2005. A factorial randomized trial compared paclitaxel versus docetaxel and weekly versus every 3 weeks schedule [14]. Overall, 4988 patients were analyzed. At a median follow-up of 46.5 months, there were no differences in disease-free survival between paclitaxel and docetaxel (HR = 0.985, CI 95% 0.84–1.15; $P = 0.83$) and between every 3 weeks versus weekly schedule (HR = 1.043, CI 95% 0.89–1.22; $P = 0.54$). An exploratory analysis showed a trend for worse outcome with three weeks paclitaxel versus weekly administration (HR = 1.20, CI 95% 0.99–1.46; $P = 0.06$). Toxicity profile showed not great differences between the two paclitaxel schedules: more neutropenia grade 3–4 was associated with 3 weeks paclitaxel (4% versus 2%), while neuropathy was typical with weekly paclitaxel (8% versus 4%).

Another exploratory analysis showed that paclitaxel given every 3 weeks is inferior to docetaxel every 3 weeks in terms of disease-free survival, even if the difference was not statistically significant (HR 1.13, CI 95% 0.94–0.36; $P = 0.20$).

Based on the results in both metastatic and early breast cancer, it seems that the best way to administer taxanes is either weekly paclitaxel or docetaxel every 3 weeks.

can taxanes substitute anthracyclines in the adjuvant setting?

A recent trial compared four cycles of AC regimen with four cycles of TC (docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2) [16]. After a median follow-up of 66 months, TC was associated with a statistical improvement in disease-free survival (HR = 0.67, $P = 0.01$), with a favorable trend in overall survival (HR = 0.76, $P = 0.13$). TC regimen was associated with more incidence of febrile neutropenia (6% versus 3%, $P = 0.03$), edema, myalgia and arthralgia of every grade but with less nausea and vomiting grade 3–4 (2% versus 7% and <1% versus 5%, respectively).

The role of taxanes instead of anthracyclines is also under evaluation in HER2-positive disease. The BCIRG 006 [17] trial compared the efficacy of two different chemotherapy regimens associated to trastuzumab. The first one was a classical AC followed by docetaxel plus trastuzumab (AC–TH), the second regimen was docetaxel and carboplatin given concurrently with trastuzumab (TCH). This trial was designed in order to reduce/avoid the cardiotoxicity induced by the combination of anthracyclines and trastuzumab. After a median follow-up of 23 months, there was no statistically significant difference between the two trastuzumab-containing arms. However, a favorable trend in disease-free survival for the anthracycline-based arm was observed (98 versus 77 events, $P = 0.16$). There was more cardiotoxicity in the AC–TH arm compared with the TCH arm. Clinically significant cardiac events were 2.34% (CI 95% 1.52–3.44) and 1.33% (CI 95% 0.73–2.21) in the AC–TH and TCH arms, respectively. Asymptomatic decline of LVEF (>10%) was significantly higher in the AC–TH arm compared with the TCH arm (17.3% versus 8.0%, respectively). One interesting finding of this trial was that 35% HER2-positive breast cancer are associated with amplification of topoisomerase II-α, the therapeutic target of anthracyclines. In amplified diseases, the use of anthracyclines was more effective than its non-use, while results between the two arms were comparable if topoisomerase II-α was not amplified.

The suggestion of these trials is that TCH in HER2-positive patients and TC in HER2-negative patients represent a treatment option, instead of anthracyclines, in a selected group of patients.

taxanes efficacy and hormonal receptor status

The EBCTCG (Early Breast Cancer Trialists' Collaborative Group) [18] evaluated the impact of polichemotherapy versus no adjuvant treatment in young (<50 years) and older (50–69 years) women in terms of recurrence and mortality. The absolute benefit at 15 years appears to be about three times as great for younger than for older women. In fact, between patients <50 years the absolute reduction of recurrence at 15 years was 12.3%, while in older women it was 4.1%. Absolute reduction of death was 10.0% in younger patients, 3.0% in older patients.

In younger women, polichemotherapy versus no adjuvant therapy is equally effective in ER-poor as well as in ER-positive disease, with a reduction of death risk of more than 30%. In older women, polichemotherapy is more effective in ER-poor than in ER-positive disease, 26% versus 5%, respectively. However, differences exist based on the type of chemotherapy used. If we consider the benefit of anthracyclines compared to CMF, the proportional effect on breast cancer mortality is independent from ER status. Among younger women, anthracyclines reduce breast cancer mortality of 39% and 36% in ER-poor and ER-positive disease, respectively (difference 2p = 0.7), whereas among older women the benefit is 24% and 19% in ER-poor and ER-positive, respectively (difference 2p = 0.5).

On the other hand, results of subgroups analysis regarding taxanes efficacy by hormonal receptor status are at least heterogeneous. BCIRG 001 and GEICAM 9906 demonstrated better efficacy of taxanes regardless of hormonal receptor status. CALGB 9344 indicated that taxanes efficacy was evident only in negative or unknown hormonal receptors patients. Paradoxically, NSABP B-28 reported a statistically significant benefit in terms of disease-free survival (HR = 0.77; CI 95% 0.65–0.92; $P = 0.004$) only in positive hormonal receptors. Of note the chemotherapy regimen used in the CALGB and NSABP trials was quite similar. Overall, hormonal receptor status seems not to be a predictive factor on which the choice of chemotherapy regimen should be based.

In conclusion, enough data are available to set taxanes as a standard treatment for node-positive early breast cancer patients. Studies are required in node-negative disease. Weekly paclitaxel and every 3 weeks docetaxel seem to be the better choice among the various taxane schedules. Hormonal receptor status cannot be a guide to choice among the various chemotherapy regimen.

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